

Food and Drug Administration, HHS

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(10) Parenteral drug products in plastic containers.

(11) Sterilization of drugs by irradiation.

(12) Sweet spirits of nitre drug products.

(13) Thorium dioxide for drug use.

(14) Timed release dosage forms.

(15) Vinyl chloride as an ingredient, including propellant, in aerosol drug products.

(b) [Reserved]

[62 FR 12084, Mar. 14, 1997, as amended at 64 FR 401, Jan. 5, 1999]

§ 310.503 Requirements regarding certain radioactive drugs.

(a) On January 8, 1963 (28 FR 183), the Commissioner of Food and Drugs exempted investigational radioactive new drugs from part 312 of this chapter provided they were shipped in complete conformity with the regulations issued by the Nuclear Regulatory Commission. This exemption also applied to investigational radioactive biologics.

(b) It is the opinion of the Nuclear Regulatory Commission, and the Food and Drug Administration that this exemption should not apply for certain specific drugs and that these drugs should be appropriately labeled for uses for which safety and effectiveness can be demonstrated by new drug applications or through licensing under the Public Health Service Act (42 U.S.C. 262 *et seq.*) in the case of biologics. Continued distribution under the investigational exemption when the drugs are intended for established uses will not be permitted.

(c) Based on its experience in regulating investigational radioactive pharmaceuticals, the Nuclear Regulatory Commission has compiled a list of reactor-produced isotopes for which it considers that applicants may reasonably be expected to submit adequate evidence of safety and effectiveness for use as recommended in appropriate labeling. Such use may include, among others, the uses in this tabulation:

Isotope	Chemical form	Use
Chromium 51 ...	Chromate	Spleen scans.
Dodo	Placenta localization.

Isotope	Chemical form	Use
Dodo	Red blood cell labeling and survival studies.
Do	Labeled human serum albumin.	Gastrointestinal protein loss studies.
Dodo	Placenta localization.
Do	Labeled red blood cells.	Do.
Cobalt 58 or Cobalt 60.	Labeled cyanocobalamin.	Intestinal absorption studies.
Gold 198	Colloidal	Liver scans.
Dodo	Intracavitary treatment of pleural effusions and/or ascites.
Dodo	Interstitial treatment of cancer.
Iodine 131	Iodide	Diagnosis of thyroid functions.
Dodo	Thyroid scans.
Dodo	Treatment of hyperthyroidism and/or cardiac dysfunction.
Dodo	Treatment of thyroid carcinoma.
Do	Iodinated human serum albumin.	Blood volume determinations.
Dodo	Cisternography.
Dodo	Brain tumor localization.
Dodo	Placenta localization.
Dodo	Cardiac scans for determination of pericardial effusions.
Do	Rose Bengal	Liver function studies.
Dodo	Liver scans.
Do	Iodopyracet, sodium iodohippurate, sodium diatrizoate, diatrizoate methylglucamine, sodium diprotrizoate, sodium acetrizoate, or sodium iothalamate.	Kidney function studies and kidney scans.
Do	Labeled fats and/or fatty acids.	Fat absorption studies.
Do	Cholografin	Cardiac scans for determination of pericardial effusions.
Do	Macroaggregated iodinated human serum albumin.	Lung scans.
Do	Colloidal microaggregated human serum albumin.	Liver scans.
Iodine 125	Iodide	Diagnosis of thyroid function.
Do	Iodinated human serum albumin.	Blood volume determinations.
Do	Rose Bengal	Liver function studies.

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Isotope	Chemical form	Use
Do	Iodopyracet, sodium iodohippurate, sodium diatrizoate, diatrizoate methylglucamine, sodium diprotrizoate, sodium acetrizoate, or sodium iothalamate.	Kidney function studies.
Do	Labeled fats and/or fatty acids.	Fat absorption studies.
Iron 59	Chloride, citrate and/or sulfate.	Iron turnover studies.
Krypton 85	Gas	Diagnosis of cardiac abnormalities.
Mercury 197 ...	Chlormerodrin	Kidney scans.
Dodo	Brain scans.
Mercury 203 ¹do	Kidney scans.
Dodo	Brain scans.
Phosphorus 32	Soluble phosphate ..	Treatment of polycythemia vera.
Dodo	Treatment of leukemia and bone metastasis.
Do	Colloidal chromic phosphate.	Intracavitary treatment of pleural effusions and/or ascites.
Dodo	Interstitial treatment of cancer.
Potassium 42 ..	Chloride	Potassium space studies.
Selenium 75 ...	Labeled methionine	Pancreas scans.
Strontium 85 ...	Nitrate or chloride ...	Bone scans on patients with diagnosed cancer.
Technetium 99m.	Pertechnetate	Brain scans.
Dodo	Thyroid scans.
Do	Sulfur colloid	Liver and spleen scans.
Do	Pertechnetate	Placenta localization.
Dodo	Blood pool scans.
Dodo	Salivary gland scans.
Do	Diethylenetriamine pentaacetic acid (DTPA).	Kidney scans.
Xenon 133	Gas	Diagnosis of cardiac abnormalities. Cerebral blood-flow studies. Pulmonary function studies. Muscle bloodflow studies.

¹This item has been removed from the AEC list for kidney scans but is included as the requirements of this order are applicable. Starttime Tuesday, April 20, 1999 16:55:11

(d)(1) In view of the extent of experience with the isotopes listed in paragraph (c) of this section, the Nuclear Regulatory Commission and the Food and Drug Administration conclude that such isotopes should not be distributed under investigational-use labeling when they are actually intended for use in medical practice.

(2) The exemption referred to in paragraph (a) of this section, as applied to

any drug or biologic containing any of the isotopes listed in paragraph (c) of this section, in the “chemical form” and intended for the uses stated, is terminated on March 3, 1972, except as provided in paragraph (d)(3) of this section.

(3) The exemption referred to in paragraph (a) of this section, as applied to any drug or biologic containing any of the isotopes listed in paragraph (c) of this section, in the “chemical form” and intended for the uses stated, for which drug a new drug application or a “Investigational New Drug Application” was submitted prior to March 3, 1972, or for which biologic an application for product license or “Investigational New Drug Application” was submitted prior to March 3, 1972, is terminated on August 20, 1976, unless an approvable notice was issued on or before August 20, 1976, in which case the exemption is terminated either upon the subsequent issuance of a nonapprovable notice for the new drug application or on November 20, 1976, whichever occurs first.

(e) No exemption from section 505 of the act or from part 312 of this chapter is in effect or has been in effect for radioactive drugs prepared from accelerator-produced radioisotopes, naturally occurring isotopes, or nonradioactive substances used in conjunction with isotopes.

(f)(1) Based on its experience in regulating investigational radioactive pharmaceuticals, the Nuclear Regulatory Commission has compiled a list of reactor-produced isotopes for which it considers that applicants may reasonably be expected to submit adequate evidence of safety and effectiveness for use as recommended in appropriate labeling; such use may include, among others, the uses in this tabulation:

Isotope	Chemical form	Use
Fluorine 18	Fluoride	Bone imaging.
Indium-113m ...	Diethylenetriamine pentaacetic acid (DTPA).	Brain imaging; kidney imaging.
Do	Chloride	Placenta imaging; blood pool imaging.
Technetium 99m.	Human serum albumin microspheres.	Lung imaging.
Do	Diethylenetriamine pentaacetic acid (Sn).	Kidney imaging; kidney function studies.

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Isotope	Chemical form	Use
Dodo	Brain imaging.
Do	Polyphosphates	Bone imaging.
Do	Technetated aggregated albumin (human).	Lung imaging.
Do	Disodium etidronate	Bone imaging.

(2) In view of the extent of experience with the isotopes listed in paragraph (f)(1) of this section, the Nuclear Regulatory Commission and the Food and Drug Administration conclude that they should not be distributed under investigational-use labeling when they are actually intended for use in medical practice.

(3) Any manufacturer or distributor interested in continuing to ship in interstate commerce drugs containing the isotopes listed in paragraph (f)(1) of this section for any of the indications listed, shall submit, on or before August 25, 1975 to the Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, a new drug application or a "Investigational New Drug Application" for each such drug for which the manufacturer or distributor does not have an approved new drug application pursuant to section 505(b) of the act. If the drug is a biologic, a "Investigational New Drug Application" or an application for a license under section 351 of the Public Health Service Act shall be submitted to the Center for Biologics Evaluation and Research, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20014, in lieu of any submission to the Center for Drug Evaluation and Research.

(4) The exemption referred to in paragraph (a) of this section, as applied to any drug or biologic containing any of the isotopes listed in paragraph (f)(1) of this section, in the "chemical form" and intended for the uses stated, is terminated on August 26, 1975 except as provided in paragraph (f)(5) of this section.

(5)(i) Except as provided in paragraph (f)(5)(ii) of this section, the exemption referred to in paragraph (a) of this section, as applied to any drug containing any of the isotopes listed in paragraph (f)(1) of this section, in the "chemical form" and intended for the uses stated, for which drug a new drug application

or "Investigational New Drug Application" was submitted to the Center for Drug Evaluation and Research on or before August 25, 1975 is terminated on August 20, 1976, unless an approvable notice was issued on or before August 20, 1976, in which case the exemption is terminated either upon the subsequent issuance of a nonapprovable notice for the new drug application or on November 20, 1976, whichever occurs first.

(ii) The exemption referred to in paragraph (a) of this section, as applied to any biologic containing any of the isotopes listed in paragraph (f)(1) of this section in the "chemical form" and intended for the uses stated, for which biologic an application for product license or "Investigational New Drug Application" was submitted to the Center for Biologics Evaluation and Research on or before August 25, 1975 is terminated on October 20, 1976, unless an approvable notice was issued on or before October 20, 1976, in which case the exemption is terminated either upon the subsequent issuance of a nonapprovable notice for the new drug application or on January 20, 1977, whichever occurs first.

(g) The exemption referred to in paragraph (a) of this section, as applied to any drug intended solely for investigational use as part of a research project, which use had been approved on or before July 25, 1975 in accordance with 10 CFR 35.11 (or equivalent regulation of an Agreement State) is terminated on February 20, 1976 if the manufacturer of such drug or the sponsor of the investigation of such drug submits on or before August 25, 1975 to the Food and Drug Administration, Bureau of Drugs, HFD-150, 5600 Fishers Lane, Rockville, MD 20857, the following information:

- (1) The research project title;
- (2) A brief description of the purpose of the project;
- (3) The name of the investigator responsible;
- (4) The name and license number of the institution holding the specific license under 10 CFR 35.11 (or equivalent regulation of an Agreement State);
- (5) The name and maximum amount per subject of the radionuclide used;
- (6) The number of subjects involved; and

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(7) The date on which the administration of the radioactive drugs is expected to be completed.

(h) The exemption referred to in paragraph (a) of this section, as applied to any drug not referred to in paragraphs (d), (f), and (g) of this section, is terminated on August 26, 1975.

[39 FR 11680, Mar. 29, 1974, as amended at 40 FR 31307, July 25, 1975; 40 FR 44543, Sept. 29, 1975; 41 FR 35171, Aug. 20, 1976; 41 FR 42947, Sept. 29, 1976; 50 FR 8996, Mar. 6, 1985; 55 FR 11578, Mar. 29, 1990; 64 FR 56449, Oct. 20, 1999]

§ 310.509 Parenteral drug products in plastic containers.

(a) Any parenteral drug product packaged in a plastic immediate container is not generally recognized as safe and effective, is a new drug within the meaning of section 201(p) of the act, and requires an approved new drug application as a condition for marketing. An "Investigational New Drug Application" set forth in part 312 of this chapter is required for clinical investigations designed to obtain evidence of safety and effectiveness.

(b) As used in this section, the term "large volume parenteral drug product" means a terminally sterilized aqueous drug product packaged in a single-dose container with a capacity of 100 milliliters or more and intended to be administered or used intravenously in a human.

(c) Until the results of compatibility studies are evaluated, a large volume parenteral drug product for intravenous use in humans that is packaged in a plastic immediate container on or after April 16, 1979, is misbranded unless its labeling contains a warning that includes the following information:

(1) A statement that additives may be incompatible.

(2) A statement that, if additive drugs are introduced into the parenteral system, aseptic techniques should be used and the solution should be thoroughly mixed.

(3) A statement that a solution containing an additive drug should not be stored.

(d) This section does not apply to a biological product licensed under the

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Public Health Service Act of July 1, 1944 (42 U.S.C. 201).

[62 FR 12084, Mar. 14, 1997]

§ 310.515 Patient package inserts for estrogens.

(a) *Requirement for a patient package insert.* FDA concludes that the safe and effective use of drug products containing estrogens requires that patients be fully informed of the benefits and risks involved in the use of these drugs. Accordingly, except as provided in paragraph (e) of this section, each estrogen drug product restricted to prescription distribution, including products containing estrogens in fixed combinations with other drugs, shall be dispensed to patients with a patient package insert containing information concerning the drug's benefits and risks. An estrogen drug product that does not comply with the requirements of this section is misbranded under section 502(a) of the Federal Food, Drug, and Cosmetic Act.

(b) *Distribution requirements.* (1) For estrogen drug products, the manufacturer and distributor shall provide a patient package insert in or with each package of the drug product that the manufacturer or distributor intends to be dispensed to a patient.

(2) In the case of estrogen drug products in bulk packages intended for multiple dispensing, and in the case of injectables in multiple-dose vials, a sufficient number of patient labeling pieces shall be included in or with each package to assure that one piece can be included with each package or dose dispensed or administered to every patient. Each bulk package shall be labeled with instructions to the dispenser to include one patient labeling piece with each package dispensed or, in the case of injectables, with each dose administered to the patient. This section does not preclude the manufacturer or labeler from distributing additional patient labeling pieces to the dispenser.

(3) Patient package inserts for estrogens dispensed in acute-care hospitals or long-term care facilities will be considered to have been provided in accordance with this section if provided to the patient before administration of the first estrogen and every 30 days